

# Secreted glycoproteins and proteoglycans orchestrate inflammation in cardiac disease

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An abstract painting featuring thick, expressive brushstrokes. The color palette is dominated by vibrant greens, deep blues, and bright yellows, with accents of red and orange. The texture is highly tactile, with visible ridges and valleys in the paint. The composition is dense and layered, suggesting a sense of depth and movement. The word 'Valorization' is superimposed in the upper right quadrant.

# Valorization





## INTRODUCTION

Heart failure is a deadly disease affecting over 20 million people worldwide. This vast prevalence of heart disease looms the prevalence of cancer and presents a serious societal burden. Though we are currently striving to find new therapeutic strategies to treat heart failure patients, we are currently still struggling to understand the intricate changes that occur in the diseased myocardium in response to injury. Complete understanding of the intricate biology of the cardiac extracellular matrix in relation to heart failure development may prevail novel inputs to treat and cure this disease. In particular comprehending the close interaction of the cardiac extracellular matrix with the immune system as immunity is one of the driving forces behind adverse cardiac remodeling hence heart failure development.

In this thesis I demonstrate that the cardiac extracellular matrix is a very dynamic entity that is continuously changing and adapting towards its environment (Chapter 3). The constantly adapting appearance of the extracellular matrix is illustrated by small leucine rich proteoglycan Osteoglycin (Chapter 4) in myocardial infarction versus viral myocarditis. That extracellular proteins are vital for regulating tissue homeostasis is illustrated by the novel role of glycoprotein SPARC in the microvascular glycocalyx where it regulates cardiac inflammation (Chapter 5). Not only recruitment of immune cells can be controlled by the extracellular environment, also the clearance of inflammation is under control of the production of versatile extracellular glycoproteins and proteoglycans. Demonstrative of this is the influence of semaphorin 3A on the clearance of pro-inflammatory M1 macrophages during myocardial infarct healing as illustrated in Chapter 6. This thesis therefore highlights novel imperative knowledge on how the ever-changing cardiac extracellular matrix regulates inflammation in cardiac disease.

## THE EXTRACELLULAR MATRIX: MY 'HEART' TO SOCIETY

Fundamental knowledge on versatile extracellular matrix proteins in relation to cardiac inflammation exhibits a novel platform for heart failure drug development. Though drug discovery is needed for improving the treatment of heart failure patients, unravelling all biological aspects of this disease entity proceeds in time. As a clinician I feel we should value the significance of fundamental research for this purpose. Creating knowledge without thinking about practical applications is what science is all about. The pursuit for complete understanding of human biology in health and disease is imperative for drug discovery. Indeed, where micro-RNAs have already disclosed a novel layer of biological complexity in cardiac disease in the early nineties thereby introducing a tremendous nursery for drug discovery, I believe this thesis suggests that the the ever-changing and versatile proteoglycans and glycoproteins residing in the extracellular matrix impose even greater therapeutic potential.

## SCIENCE COMMUNICATION

As a clinician and person I feel strongly about clear, open and vociferous communication on our fundamental scientific findings to a layman's audience. I feel the general public should be informed about the importance of fundamental biological discoveries in order to appreciate its relevance and value for the eventual drug discovery and development. If we can go on this

quest together by increasing the commitment and involvement of society, the chance of finding that one cure for heart failure might be closer than we think. In this thesis I have tried to gather all the necessary expertise that was needed to unravel the intricacy of the studied proteins. Not only these collaborations but also conferences allow for attaining feedback from experts in the field on the obstacles one faces when unraveling the multifariousness of glycobiology. The feedback that I have received has helped me in formulating sharp hypothesis thereby facilitating the quest for answers. Fortunately this process work two ways as my presentations on conferences has also resulted in increased attention for the importance yet intricacy of glycobiology in the heart. This collective search for novel therapeutic strategies in cardiology is presented by this thesis and will hopefully aid heart failure drug development.

## THE EXTRACELLULAR MATRIX: FROM MICE TO MAN

Because the level of complexity of the extracellular matrix takes precedence over that of micro-RNA biology, unraveling the appearance of this ever-changing extracellular structure is challenging. Untying all players in the extracellular compartment and assigning individual value to each of them in the seemingly chaotic series of events that occur during disease, may help in finding an entrance to influence the outcome of the disease. However, where does one start with such an overwhelming endeavor. As we currently lack the technology to create biologically identical robots to mimic our human diseases, at present we still use animal models for this purpose. The fact that heart disease is a highly complex illness where many factor contribute to disease progression and outcome doesn't allow us to use cell culture or in silico calculation to study its pathophysiology. Nevertheless, we should strive for reducing and replacing the use of animals for scientific purposes by stimulating collaborations with researchers all over the world.

## TRANSLATION TO OTHER FIELDS

While inflammation is a major contributor to cardiac disease development and progression, it is certainly not exclusive to the myocardium. Indeed, one of the most intriguing aspects of studying inflammation is the multiplicity of the inflammatory mediators that are constantly being discovered, like microRNAs, adipokines, inflammasomes and the danger signals like extracellular glycoproteins and proteoglycans. Interestingly, their effect on target tissues seems very universal and numerous studies have demonstrated that inflammatory responses represent the 'common soil' of the multifactorial diseases, covering both chronic inflammatory rheumatic disorders as well as an extensive range of conditions including cardiovascular disease, neurodegenerative diseases, type 2 diabetes, obesity, asthma, ageing and cancer. Therefore, this thesis unravels novel inflammatory mediators that influence cardiac inflammation, hence are likely to involve general inflammatory responses.

## CONCLUSION

Heart failure is a tremendous societal burden and current therapies are mainly supportive. Hence, there is real need for finding new therapeutic strategies. Where micro-RNAs have already opened the stage for novel drug discovery, extracellular glycoproteins and proteoglycans

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are an even greater nursery for heart failure drug discovery. Fundamental findings as described in this thesis are vital in this search. Not only in cardiovascular disease do extracellular glycoproteins and proteoglycans present novel treatment possibilities, numerous diseases could benefit the multiplicity of the novel inflammatory mediators described in this thesis. Finally, as a clinician, I would like to emphasize that this thesis shows that fundamental research is an inseparable keystone in drug discovery.